UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/723,722	11/28/2000	John P. Anderson	00228-US-NEW2C1	9856

21835 7590 02/20/2004

ELAN PHARMACEUTICALS, INC.
INTELLECTUAL PROPERTY DEPARTMENT
800 GATEWAY BOULEVARD
SOUTH SAN FRANCISCO, CA 94080

EXAMINER	
WALICKA, MALGORZATA A	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 02/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/723,722	ANDERSON ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15,18,19,22-25,27-37,39-53,132 and 133* is/are pending in the application.

4a) Of the above claim(s) *5-13, 21,37 and 39-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,15,18,22-25,29-36,132 and 133* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10 cd*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

The Amendments filed on October 29 and November 10, 2003 are acknowledged. Claims 14, 16-17, 20, 26, 32 and 54-131 are canceled. New claims 132-133 are added. Claims 1-4, 15, 18-19, 22, 23, 27 are amended. Claims 1-13, 15, 18-19, 22-25, 27-37, and 39-53 and 132-133 are pending in the application. Claims 1-4, 15, 18, 22-25, 29-36 and 132-133 are the subject of this Office Action.

DETAILED ACTION

1. Restriction/election

Claim 15 drawn to the elected invention of SEQ ID NO: 43 was inadvertently excluded from the first Office Action on merits. The claim is examined in this Office Action.

The scope of claims 19, 27 and 28 does not include SEQ ID NO: 43, therefore the claims are withdrawn from consideration as not reading on the elected species of SEQ ID NO: 43.

2. Objections

2.1. Specification

Although the description of Fig. 5 on page 8 is now clear as to the term "proenzyme" the filed amendment to the specification is confusing in recitation "the polynucleotide region corresponding to the active enzyme portion corresponding to amino acids 46-501 SEQ ID NO: 43) (nt 135-1503) is shown as SEQ ID NO: 44."

SEQ ID NO: 44 consists of 2348 and not of 1369 nt; it is unclear what SEQ ID NO: 44 encodes.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors in the specification of which applicant may become aware.

2.2. Claims

Claims 15, 23, 24, 25 are objected to for the improper quotation of the amino acid residues, e.g., [46—501]. The correct quotation is "amino acid residues 46-501 of SEQ ID NO: 2."

Claim 25 contains a typographical error "SEQ ID NO: 43 [46-452]". SEQ ID NO: 43 consists of amino acids 46-501 of SEQ ID NO: 2.

3. Rejections

3.1. 35 USC, section 112, second paragraph

Rejection of claims 18 and 27-36 for not further limiting the base claim 1 and 23 is withdrawn, because claim 1 has been amended.

Claims 2, 132 and 133 recite the limitation "the enzyme". There is insufficient antecedent basis for this limitation in the claims, because base claim 1 is directed to a protein and not to an enzyme.

Claim 132 is rejected because it does not further limit claim 1 from which it depends. If a protein is purified to apparent homogeneity it runs as a single band on a

SDS PAGE gel under reducing conditions"; see definition of "to be purified to apparent homogeneity" on page 18, line 1.

Claim 133 is rejected because the claim does not further limit claim 1 from which depends. The limitation "wherein the enzyme has been purified sufficiently to provide a suitable substrate for N-terminal amino acid determination" is already included in the limitation "purified to apparent homogeneity". The homogenous protein is the one that must be used for determination of its N terminal amino acid sequence.

3.2. 35 USC section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3.2.1. Lack of written description

Claim 1 and dependent claims 2-4, 22, 23, 24, 29-36, and 132-133 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to any protein purified to apparent homogeneity comprising a segment of any beta-secretase protein, wherein the segment lacks the signal sequence (amino acids residues 1-22 with respect to SEQ ID NO: 2) and the putative proregion (amino acid residues 23-45 with respect to SEQ ID NO: 2). Thus, the claims are directed to a large and variable genus of proteins for which there is no sufficient written description in the disclosure. The scope of the claims encompasses proteins comprising fragments of any beta- secretase protein wherein said fragments do not contain the signal sequence and proregion which are amino acid residues 1-45 with respect to human beta secretase of SEQ ID NO: 2 disclosed by Applicants. There is insufficient description of the structure and function of the genus of proteins towards which the claims are directed.

The claims do not state the function of the claimed genus of proteins. Examiner understands that the desired function is that of beta-secretase. The specification discloses several species of said genus, i.e. proteins identified by SEQ ID NOs: 43, 58, 67, 68, 69, 70, 71, 75 for which the structure and function are known. These species, however, cannot identify the whole genus of the claimed proteins because said genus comprises proteins that do not have a beta-secretase activity or may have other enzymatic activity or no activity at all. For example, if a protein comprises a fragment of beta-secretase of SEQ ID NO: 2 consisting of amino acid residues 46-50, the protein will not have the enzymatic activity of a beta-secretase. Furthermore, although the

disclosure teaches that the fragment of beta- secretase of SEQ ID NO: 2 consisting of amino acids 63-419 has the desired enzymatic activity, there is nothing to suggests that shorter fragments do not posses said activity. The applicants do not disclose the structure/function relationship for the genus of the claimed proteins.

In addition, the claims read on proteins comprising fragments of any beta-secretase including all known and unknown natural animal variants and man-made beta-secretases. As the sequence of these beta-secretases are not disclosed, one skilled in the art does not know whether the signal sequences and putative proregion sequences are present in all beta- secretases, and, if they are present, how many amino acids they comprise.

In conclusion, one skilled in the art is not reasonably convinced that that the inventor(s), at the time the application was filed, had possession of the claimed invention.

3.2.2. Scope of enablement

Claim 1-4, 22, 23, 24, 26-36, and 132-133 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NOs: 43, 58, 67, 68, 69, 70, 71, 75, does not reasonably provide enablement for any purified protein comprising a segment of a beta-secretase protein, wherein the segment lacks the signal sequence (amino acids residues 1-22 with respect to SEQ ID NO: 2) and the putative proregion (amino acid residues 23-45 with respect to SEQ ID NO:2). The specification does not enable any person skilled in the art to which it pertains, or with which it is most

nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are broader than the enablement provided by the disclosure with regard to the extremely large number of polypeptides covered by the scope of the claims; see the above rejection for lack of written description. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the nature of the invention, (b) the breadth of the claim, (c) the state of the prior art, (d) the relative skill of those in the art, (e) the predictability of the art, (f) the presence or absence of working example, (g) the amount of direction or guidance presented, (h) the quantity of experimentation necessary.

The nature and breath of the claimed invention encompasses any purified protein comprising a segment of any beta-secretase protein originating from any natural source or man-made, wherein the segment lacks the signal sequence (amino acids residues 1-22 with respect to SEQ ID NO: 2) and the putative proregion (amino acid residues 23-45 with respect to SEQ ID NO:2).

While methods of gene cloning and gene structure manipulations are well known in the relevant art, and skills of the artisans sufficiently developed to enable cloning all unknown genes encoding beta secretase and make the DNA constructs

encoding the claimed proteins, the outlined experimentation is out of the realm of the routine experimentation. The further experiments are necessary to construct DNA encoding proteins of invention wherein said construct encode proteins containing fragments on known beta-secretases. The specification provides examples of the species of the genus by disclosure of polypeptides identified by SEQ ID NOs: 43, 58, 67, 68, 69, 70, 71, 75. These proteins, however, do not provide an identifying characteristics of the whole genus. Thus making the proteins belonging to the claimed genus has a low probability of success absent the functional and structural characteristics of said genus.

Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. Examiner concludes that without the further guidance on the part of Applicants with respect to the function and structure of the claimed proteins, experimentation left to those in the art is improperly extensive and undue.

3.3. 35 USC, section 102

Rejection of claim 20, as being anticipated by US patent No. 6, 420, 534, made in the previous Office Action is moot, because the claim has been cancelled. Rejection of claim 19 is moot because the claim does not read on the elected species of SEQ ID NO: 43.

Rejection of claim 18 in part related to SEQ ID NO:43 is withdrawn, because SEQ ID NO:43 is a truncated form of the beta secretase as set fort by amino acid

sequence of SEQ ID NO:2 in the instant application. The patent does not disclose the same beta secretase as that set forth by amino acid sequence of SEQ ID NO:2 in the instant application.

The amended claim 1 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by US patent No. 6,319,689, issued to Powell et al. on Nov. 20, 2001, filed on Jan 20, 1998, with priority date Jan. 28, 1997.

The claims are directed to protein purified to apparent homogeneity comprising a segment of a beta-seretase enzyme protein, wherein said segment lacks the signal sequence (amino acids residues 1-22 with respect to SEQ ID NO: 2) and the putative proregion (amino acid residues 23-45 with respect to SEQ ID NO: 2). The claims, therefore read on any beta-secretase. Powell et al. cloned the gene and disclose the SEQ ID NO: 2 encoded by said gene. The Powell et al.' SEQ ID NO: 2 is a human beta-secretase of 501amino acids having in position 130 glutamine, whereas SEQ ID NO: 2 in of the instant application has in position 130 valine. SEQ ID NO: 2 of the patent comprises a segment of a beta-secretase enzyme protein, i.e. segments of SEQ ID NO: 2 of the patent, wherein said segment lacks amino acids 1- 45 with respect to SEQ ID NO: 2 of the instant application.

In addition, Powell et al teach, column 15, line 14, purification of the expressed beta-secretase and, column 14, line 27, production of beta-secretase of SEQ ID NO: 2 in heterologous host cells. Thus the patent teaches all elements of claim 1 and 22 of the instant application.

Powell teaches, "ASP2 polypeptides can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lecitin chromatography. Most preferably, high performance liquid chromatography is employed for purification" (column 15, line 14). One skilled in the art recognize that the purification methods taught by Powell allow for purification of proteins to apparent homogeneity.

Traversing the rejection under 102 made in the previous Office Action Applicants state: "Powell excludes at least one element that is set forth in Applicants' claims 1-4, 18, 19, and 22. Claims 1 and 22 are directed to a protein having a valine at residue 130. Powell does not disclose such an amino acid sequence."

Applicants' argument has been fully considered, but is found not persuasive. The amended claims 1 and 22 are not limited to the proteins comprising fragments of beta-secretase of SEQ ID NO:2 of the instant application. The claims are directed to any purified protein comprising a segment of any beta-secretase protein, wherein the segment lacks the signal sequence (amino acids residues 1-22 with respect to SEQ ID NO: 2) and the putative proregion (amino acid residues 23-45 with respect to SEQ ID NO: 2).

3.4. 35 USC section 103

Rejection of claims 24-25 made in the previous Office Action over US Patent No. 6,319,689 is withdrawn because it was improper. The patent does not teach SEQ ID NO:43 and 71. Rejection of claim 27-28 made in the previous Office Action is moot, because the claims do not read on the elected invention of SEQ ID NO: 43. Rejection of claims 31-36 was improper because Powell et al do not disclose or suggest compositions of beta sectretase and its substrate or inhibitor, particularly inhibitors recited by claims 32-36.

Claims 23 and 29-30 are still rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,319,689, issued to Powell et al.; see the above rejection under 35 USC section 102, in view of the common knowledge in molecular biology.

Claims 23 and 29-30 are directed to crystalline compositions of a protein wherein

(1) said protein comprising a segment of any beta-secretase protein, wherein the segment lacks the signal sequence (amino acids residues 1-22 with respect to SEQ ID NO: 2) and the putative proregion (amino acid residues 23-45 with respect to SEQ ID NO: 2),

(2) said protein is purified to apparent homogeneity,

(3) said protein is glycosylated or non-glycosylated, and wherein

(4) said protein is in crystalline form.

Regarding point 1) as discussed above, the US Patent No. 6,319,689 discloses

an isolated protein comprising a segment of a beta-secretase protein, wherein the segment lacks the signal sequence (amino acids residues 1-22 with respect to SEQ ID NO: 2) and the putative proregion (amino acid residues 23-45 with respect to SEQ ID NO: 2).

Regarding point 2) Powell teaches, "ASP2 polypeptides can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lecitin chromatography. Most preferably, high performance liquid chromatography is employed for purification" (column 15, line 14). One skilled in the art recognize that the purification methods taught by Powell allow for purification of proteins to apparent homogeneity.

With respect to point (3) Powell et al. teach expression of the beta-secretase protein in bacterial cells, which results in nonglycosylated protein or in mammalian cells, which results in glycosylated protein; see column 14, line 41 of the patent.

Powell, however, does not disclose the composition of beta-secretase wherein the protein is in crystalline form.

It would have been obvious to one having ordinary skill in the art at the time of invention to have the composition of protein taught by Powell and modify it by crystallization. The motivation that is obvious to one having ordinary skill in the art is to have the composition that is in more stable form than dissolved protein and the

composition that enables crystallographic studies of interaction between the enzyme and its substrate with the purpose of studies on interaction of the enzyme and substrate. One skilled in the are would have been also motivated to make a crystalline composition of enzyme and its with inhibitor for the purpose of studies of interaction of the enzyme with inhibitor. Yet another motivation is provided by Powell et al. who write in column 19, line 28: "This invention provides methods of treating abnormal conditions...related both an excess and insufficient amounts of ASP2 polypeptide activity [beta-secretase, emphasis addeed]." In line 46 of column 19 Powell et al. write, "In another approach, soluble forms of ASP2 polypeptides still capable of binding the ligand in competition with endogenous ASP2 polypeptide may be administered." For the purpose of such administration crystalline solutions of the beta-secretase are more suitable because they are more stable, i.e. they have a longer shelf live, than soluble form of that protein and when administered to a subject in need the crystalline solution is converted in the body in a soluble form.

The probability of success in obtaining the claimed invention is 100%, because the methods of protein crystallization are routinely used in the art.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made, and was, as a whole, *prima facie* obvious.

Traversing this rejections, Applicants write in their Remarks on page 13 "the probability of success in obtaining the claim invention is 0% because Powell fails to

teach SEQ ID NO: 2 of the present application. Based on the foregoing, it is respectfully submitted that the rejection should be withdrawn."

Applicants' argument has been fully considered but is found not persuasive. The claims are not limited to SEQ ID NO: 2 of the present application, which differs in amino acid residue 130 from SEQ ID NO: 2 in Powell. The claims are directed to a protein comprising a segment of any beta-secretase protein, wherein the segment lacks the signal sequence (amino acids residues 1-22 with respect to SEQ ID NO: 2) and the putative proregion (amino acid residues 23-45 with respect to SEQ ID NO: 2). SEQ ID NO: 2 of the patent belongs to the scope of the claimed invention; see the above rejection under 35 USC, section 102.

3. 5. Double patenting rejection

3.5.1. Provisional nonstatutory double patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

It is noted that the application srial No. 09/724,569 ('569), of the same inventive entity, filed on the same day as the instant application, and claiming priority to the same applications as that of the instant application, also disclose polypeptide of SEQ ID NO: 43, which is elected by Applicants. '569 discloses also other truncated forms of beta-secretase enzyme set forth by SEQ ID NO: 2 in the instant application and compositions comprising polypeptides in crystalline form with or without inhibitors, which are disclosed also in the instant application.

Claim 1, 2, 3, 4, 18, 22, 23, 24, 25, 29 30, 31, 32, 33, 34, 36, 132 and 133 of the instant application are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1, 2, 3, 4, 18, 22, 23, 24, 25, 29 30, 31, 32, 33, 34, 36 of the '569.

An obviousness–type double patenting is appropriate where the conflicting claims are not identical, but an examined claim is either anticipated by, or would have been obvious over the reference claim(s). See e.g. *In re Berg*, 140 F.3d 1428,

46USPQ2d1226 (Fed.Cir. 1998); *In re Boodman*, 11F.3 d 1046, 29USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F. 2d 887, 225 USPO 645 (Fed. Cir. 1985).

Here, claims of 1, 2, 3, 4, 18, 22, 23, 24, 25, 29 30, 31, 32, 33, 34, 36 the instant application are directed to a protein purified to apparent homogeneity comprising a segment of any beta-secretase protein (protein involved in Alzheimer disease), wherein the segment lacks the signal sequence (amino acids residues 1-22 with respect to SEQ ID NO: 2) and the putative proregion (amino acid residues 23-45 with respect to SEQ ID NO: 2), and wherein said protein:

(2) has been purified sufficiently so that the activity of cleaving 695-amino acid isotype of beta-amyloid precursor protein between amino acids 596 and 597 thereof is at least 10,000-fold greater than solublized but unenriched membrane fraction from human 293 cells or

(3) is characterized by a specific activity of at least about 0.2 $x10^5$ nM/h/ug protein in an MBPC125sw substrate assay or

(4) wherein said specific activity in said assay is at least 1.0 $x10^5$ nM/h/ug protein or

(18) has an N-terminal residue corresponding to a residue selected from the group consisting of residues 46, 58, and 63 with respect to SEQ ID NO: 2 and a C terminus selected from a residue between positions 452 and 501 with respect to SEQ ID NO: 2 or

(22) said protein is produced by a heterologous cell.

Claims 23, 25, 29, 30, 31, 32, 33, 34, 36 the instant application are directed

to a crystalline protein composition formed from the protein purified to apparent homogeneity comprising a segment of any beta-secretase protein (protein involved in Alzheimer disease), wherein the segment lacks the signal sequence (amino acids residues 1-22 with respect to SEQ ID NO: 2) and the putative proregion (amino acid residues 23-45 with respect to SEQ ID NO: 2), and wherein said protein:

(25) has a sequence selected from the group consisting of SEQ ID NO: 43 and SEQ ID NO: 71 or

(29) is glycoslylated or

(30) is deglycosylated or

(31) wherein said composition further includes a beta-secretase substrate or inhibitor molecule

(32) wherein said beta-secretase inhibitor is a peptide having fewer than about 15 amino acids and comprises the sequence SEQ ID NO: 78, including conservative substitutions thereof or

(33) said beta-secretase inhibitor has the sequence SEQ ID NO: 72 including conservative substitutions thereof or

(34) said beta-secretase inhibitor has the sequence SEQ ID NO: 81, wherein X is hydroxyethylene or statine or

(35) said beta-secretase inhibitor is characterized by a K_i of no more than about 0.5 mM or

(36) said beta-secretase inhibitor is characterized by a K_i of no more than about 50 μM.

Claims of 1, 2, 3, 4, 18, 22, 23, 24, 25, 29 30, 31, 32, 33, 34 and 36 of '569 application are directed to a beta secretase enzyme protein (protein involved in Alzheimer disease), purified to apparent homogeneity, wherein said protein:

(2) has been purified sufficiently so that the activity of cleaving 695-amino acid isotype of beta-amyloid precursor protein between amino acids 596 and 597 thereof is at least 10,000-fold greater than solublized but unenriched membrane fraction from human 293 cells or

(3) is characterized by a specific activity of at least about 0.2 $x10^5$ nM/h/ug protein in an MBPC125sw substrate assay or

(4) wherein said specific activity in said assay is at least 1.0 $x10^5$ nM/h/ug protein or

(18) has an N-terminal residue corresponding to a residue selected from the group consisiting of residues 22, 46, 58, and 63 with respect to SEQ ID NO: 2 and a C terminus selected from a residue between positions 452 and 501 with respect to SEQ ID NO: 2 or

(22) said protein is produced by a heterologous cell.

Claims 23, 25, 29, 30, 31, 32, 33, 34, 36 the '569 application are directed to a crystalline protein composition formed from a beta-secretase protein purified to apparent homogeneity, wherein said protein:

(25) has a sequence selected from the group consisting of SEQ ID NO: 66, SEQ ID NO: 43, SEQ ID NO: 74, and SEQ ID NO: 71 or

(29) is glycoslylated or

(30) is deglycosylated or

(31) wherein said composition further includes a beta-secretase substrate or inhibitor molecule

(32) wherein said beta-secretase inhibitor is a peptide having fewer than about 15 amino acids and comprises the sequence SEQ ID NO: 78, including conservative substitutions thereof or

(33) said beta-secretase inhibitor has the sequence SEQ ID NO: 72 including conservative substitutions thereof or

(34) said beta-secretase inhibitor has the sequence SEQ ID NO: 81, wherein X is hydroxyethylene or statine or

(35) said beta-secretase inhibitor is characterized by a K_i of no more than about 0.5 mM or

(36) said beta-secretase inhibitor is characterized by a K_i of no more than about 50 μM.

Claim 1 of '569 application is a species of the genus of proteins toward which claim 1 of the instant application is directed. Claim 1 of the instant application comprises all beta secretases. Claim 1 of the instant application is thus anticipated by claim 1 of the '569 application, because a genus is anticipated by a species. Dependent claims 2, 3, 4 and 22 of the instant application and of the '569 application contain the same set of limitations, thus claims of the instant application are anticipated

by claims of '569 because independent claim 1 of the instant application is anticipated by the independent claim 1 of the '569 application.

Claim 18 of the instant application is directed to two particular species of claim 18 of '569 application, thus claim 18 of the instant application is obvious over claim 18 of the '569 application.

Claim 23 of '569 application is directed to a composition which is a species of the genus of compositions of claim 23 of the instant application. Claim 23 of the instant application is thus anticipated by claim 23 of the '569 application, because a genus is anticipated by a species. Dependent claims 29, 30, 31, 32, 33, 34, 36 of the instant application and dependent claims 29, 30, 31, 32, 33, 34, 36 of the '569 application contain the same set of limitations. Thus claims of the instant application are anticipated by claims of '569 because independent claim 1 of the instant application is anticipated by the independent claim 1 of the '569 application.

Claim 25 of the instant application is directed to two particular species (SEQ ID NOs: 43 and 71) of the genus of species SEQ ID NO: 66, SEQ ID NO: 43, SEQ ID NO: 74, and SEQ ID NO: 71 of claim 25 of '569 application. Thus claim 25 of the instant application is obvious over claim 25 of '569 application.

In addition, claims 132 and 133 of the instant application are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of ' 569 application.

Claims 132 and 133 are directed to a protein purified to apparent homogeneity comprising a segment of a beta-secretase protein, wherein the segment lacks the signal sequence (amino acids residues 1-22 with respect to SEQ ID NO: 2) and the putative proregion (amino acid residues 23-45 with respect to SEQ ID NO: 2), wherein the enzyme has been purified sufficiently to run as a single band on a SDS PAGE gel under reducing conditions (claim 132) or wherein the enzyme has been purified sufficiently to provide a suitable substrate for N-terminal amino acid determination (claim 133).

Claim 132 is anticipated by claim 1 of '569 application, because claim 1 of '569 is entirely in the scope of claim 132 of the instant application. Claim 1 of '569 application is a species of the proteins towards which claim 132 is directed; see above. The limitation "purified sufficiently to run as a single band on a SDS PAGE gel under reducing conditions" is already included in the limitation "purified to apparent homogeneity."

Claim 133 is anticipated by claim 1 of the'569 application, because claim 1 of '569 is entirely in the scope of claim 132 of the instant application. Claim 1 of '569 application is a species of the proteins towards which claim 132 is directed; see above. The limitation "wherein the enzyme has been purified sufficiently to provide a suitable substrate for N-terminal amino acid determination" is already included in the limitation "purified to apparent homogeneity."

3.5.2. Nonstatutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 and 2 of the instant application are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1, 2 and 6 of U.S. Patent No. 5,744,346 in view of common knowledge in the molecular biology.

An obviousness–type double patenting is appropriate where the conflicting claims are not identical, but an examined claim is either anticipated by, or would have been obvious over the reference claim(s). See e.g. *In re Berg*, 140 F.3d 1428,

46USPQ2d1226 (Fed.Cir. 1998); *In re Boodman*, 11F.3 d 1046, 29USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F. 2d 887, 225 USPO 645 (Fed. Cir. 1985).

Here, claim 1 is directed to a protein purified to apparent homogeneity comprising a segment of any beta-secretase protein (protein involved in Alzheimer disease), wherein the segment lacks the signal sequence (amino acids residues 1-22 with respect to SEQ ID NO: 2) and the putative proregion (amino acid residues 23-45 with respect to SEQ ID NO: 2). Claim 2 is directed to protein of claim 1, wherein said protein has been purified sufficiently so that the activity of cleaving 695-amino acid isotype of beta-amyloid precursor protein between amino acids 596 and 597 thereof is at least 10,000-fold greater than solublized but unenriched membrane fraction from human 293 cells. Claim 1 and 2 read on any beta-secretase purified to apparent homogeneity.

Claims 1, 2 and 6 of the patent are directed to isolated beta secretase having the ability to cleave the 695- amino acid isotype of beta-amyloid precursor protein between amino acids 596 and 597 and

1) having apparent molecular weight in the range 260-300 KDa,

2) having apparent molecular weight in the range 260-300 KDa and being isolated from human brain tissue or human 293 cells ATCC CRL 1573,

6) having apparent molecular weight in the range 260-300 KDa and being purified sufficiently to have the cleavage activity at least 100–folder than that of a solublized but unenriched membrane fraction from human 293 cells.

The beta secretase enzyme isolated from mammalian cell is in a mature form, i.e. does not posses the signal region or proregion, thus claim 1, 2 and 6 of the patent are directed to the proteins that would be species of the genus claimed in claim 1 and 2 if not for the fact that although the proteins of claim 1, 2 and 6 of the patent are purified, they are not purified to the apparent homogeneity.

The patent teaches, "purification of the putative beta-secretase enzyme would permit chemical modeling of a critical event in the pathology of Alzheimer's disease and would allow the screening of compounds to determine their ability to inhibit beta-secretase activity" (column 1, line 34).

One skilled in the art realizes that identifying inhibitors of the enzyme is the more efficient the purer the protein. Therefore, it would have been obvious to modify the invention disclosed in the patent, by purification the protein to apparent homogeneity, so that it had activity at least 10,000-foldgreater than unenriched membrane fraction from human 293 cells. One having ordinary skills in the art would have been motivated to purify the protein to apparent homogeneity to optimize chemical modeling of critical events in the pathology of Alzheimer disease and screening for the enzyme inhibitors, as per common knowledge in molecular biology and supporting fragments of U.S. Patent No. 5,744,346.

3.5.3. Provisional statutory double patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or

discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 15 and 24 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 15 and 24 of copending Application No. 09724,569. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

4. Conclusion

No claim is in condition for allowance.

The following is examiner's reason for stating the allowable subject matter. The invention relates to beta-secretase, which is the enzyme highly implicated in the etiology of the Alzheimer disease. The Applicants are the first to disclose and characterize one of the mutant form of human beta-secretase of unique amino acid sequence set forth by SEQ ID NO: 2. The closest prior art is the US patent No. 6,319,689 disclosing another

variant of human beta secretase consisting also of 501 amino acids, but having in position 130 glutamine and not valine as is the case in the instant application.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0944 and the right fax number is (571) 273-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m. EST.

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1800

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-0928. The fax phone number for this Group is (703)872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Art Unit 1652

Patent Examiner

REBECCA E. PRUTY
PRIMARY EXAMINER
GROUP ~~1600~~ 1652